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Oncology

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Full Prescribing Information

Herceptin® (Trastuzumab)

Printer

WARNINGS:
CARDIOMYOPATHY

HERCEPTIN administration can result in the development of ventricular dysfunction and congestive heart failure ventricular function should be evaluated in all patients prior to and during treatment with HERCEPTIN. Discontin HERCEPTIN treatment should be strongly considered in patients who develop a clinically significant decrease in ventricular function. The incidence and severity of cardiac dysfunction was particularly high in patients who recei HERCEPTIN in combination with anthracyclines and cyclophosphamide. (See WARNINGS.)

HYPERSENSITIVITY REACTIONS INCLUDING ANAPHYLAXIS
INFUSION REACTIONS
PULMONARY EVENTS

HERCEPTIN administration can result in severe hypersensitivity reactions (including anaphylaxis), infusion react pulmonary events. Rarely, these have been fatal. In most cases, symptoms occurred during or within 24 hours o administration of HERCEPTIN. HERCEPTIN infusion should be interrupted for patients experiencing dyspnea or significant hypotension. Patients should be monitored until signs and symptoms completely resolve. Discontinua HERCEPTIN treatment should be strongly considered for patients who develop anaphylaxis, angioedema, or act distress syndrome. (See WARNINGS.)

DESCRIPTION
HERCEPTIN (Trastuzumab) is a recombinant DNA-derived humanized antibody that selectively binds with high af based assay (Kd = 5 nM) to the extracellular domain of the human epidermal growth factor receptor 2 protein, HEI antibody is an IgG1 kappa that contains human framework regions with the complementarity-determining regions antibody (4D5) that binds to HER2.

The humanized antibody against HER2 is produced by a mammalian cell (Chinese Hamster Ovary) [CHO] susper a nutrient medium containing the antibiotic gentamicin. Gentamicin is not detectable in the final product.

HERCEPTIN is a sterile, white to pale yellow, preservative-free lyophilized powder for intravenous (IV) administrat nominal content of each HERCEPTIN vial is 440 mg Trastuzumab, 9.9 mg L-histidine HCl, 6.4 mg L-histidine, 400 trehalose dihydrate, and 1.8 mg polysorbate 20, USP. Reconstitution with **only 20 mL of the supplied Bacterios Injection (BWFI)**, USP, containing 1.1% benzyl alcohol as a preservative, yields a multi-dose solution containing : Trastuzumab, at a pH of approximately 6.

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CLINICAL PHARMACOLOGY

General

The HER2 (or c-erbB2) proto-oncogene encodes a transmembrane receptor protein of 185 kDa, which is structura the epidermal growth factor receptor.[1] HER2 protein overexpression is observed in 25%-30% of primary breast ca protein overexpression can be determined using an immunohistochemistry-based assessment of fixed tumor bloc

Trastuzumab has been shown, in both *in vitro* assays and in animals, to inhibit the proliferation of human tumor ce overexpress HER2.[4-6]

Trastuzumab is a mediator of antibody-dependent cellular cytotoxicity (ADCC).[7-8] *In vitro*, HERCEPTIN-mediated been shown to be preferentially exerted on HER2 overexpressing cancer cells compared with cancer cells that do overexpress HER2.

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Pharmacokinetics

The pharmacokinetics of Trastuzumab were studied in breast cancer patients with metastatic disease. Short durat infusions of 10 to 500 mg once weekly demonstrated dose-dependent pharmacokinetics. Mean half-life increased decreased with increasing dose level. The half-life averaged 1.7 and 12 days at the 10 and 500 mg dose levels, re Trastuzumab's volume of distribution was approximately that of serum volume (44 mL/kg). At the highest weekly c (500 mg), mean peak serum concentrations were 377 microgram/mL.

In studies using a loading dose of 4 mg/kg followed by a weekly maintenance dose of 2 mg/kg, a mean half-life of = 1 to 32 days) was observed. Between Weeks 16 and 32, Trastuzumab serum concentrations reached a steady trough and peak concentrations of approximately 79 microgram/mL and 123 microgram/mL, respectively.

Detectable concentrations of the circulating extracellular domain of the HER2 receptor (shed antigen) are found in some patients with HER2 overexpressing tumors. Determination of shed antigen in baseline serum samples revea (286/447) of patients had detectable shed antigen, which ranged as high as 1880 ng/mL (median = 11 ng/mL). Pa higher baseline shed antigen levels were more likely to have lower serum trough concentrations. However, with w most patients with elevated shed antigen levels achieved target serum concentrations of Trastuzumab by Week 6

Data suggest that the disposition of Trastuzumab is not altered based on age or serum creatinine (up to 2.0 mg/dl interaction studies have been performed.

Mean serum trough concentrations of Trastuzumab, when administered in combination with paclitaxel, were consi approximately 1.5-fold as compared with serum concentrations of Trastuzumab used in combination with anthracy cyclophosphamide. In primate studies, administration of Trastuzumab with paclitaxel resulted in a reduction in Tra clearance. Serum levels of Trastuzumab in combination with cisplatin, doxorubicin or epirubicin plus cyclophospha suggest any interactions; no formal drug interaction studies were performed.

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CLINICAL STUDIES

The safety and efficacy of HERCEPTIN were studied in a randomized, controlled clinical trial in combination with (469 patients) and an open-label single agent clinical trial (222 patients). Both trials studied patients with metastati whose tumors overexpress the HER2 protein. Patients were eligible if they had 2+ or 3+ levels of overexpression 3+ scale) by immunohistochemical assessment of tumor tissue performed by a central testing lab.

A multicenter, randomized, controlled clinical trial was conducted in 469 patients with metastatic breast cancer wh previously treated with chemotherapy for metastatic disease.[9] Patients were randomized to receive chemotherapy combination with HERCEPTIN given intravenously as a 4 mg/kg loading dose followed by weekly doses of HERC mg/kg. For those who had received prior anthracycline therapy in the adjuvant setting, chemotherapy consisted of mg/m^2 over 3 hours every 21 days for at least six cycles); for all other patients, chemotherapy consisted of anthra cyclophosphamide (AC: doxorubicin 60 mg/m^2 or epirubicin 75 mg/m^2 plus 600 mg/m^2 cyclophosphamide every 2 cycles). Compared with patients in the AC subgroups (n = 281), patients in the paclitaxel subgroup (n = 188) were have had the following: poor prognostic factors (premenopausal status, estrogen or progesterone receptor negativ positive lymph nodes), prior therapy (adjuvant chemotherapy, myeloablative chemotherapy, radiotherapy), and a free interval. Sixty-five percent of patients randomized to receive chemotherapy alone in this study received Herce of disease progression as part of a separate extension study.

Compared with patients randomized to chemotherapy alone, the patients randomized to HERCEPTIN and chemo experienced a significantly longer median time to disease progression, a higher overall response rate (ORR), a lo duration of response, and a longer median survival. (See Table 1.) These treatment effects were observed both in received HERCEPTIN plus paclitaxel and in those who received HERCEPTIN plus AC, however the magnitude of greater in the paclitaxel subgroup. The degree of HER2 overexpression was a predictor of treatment effect. (See CLINICAL STUDIES: *HER2 protein overexpression*.)

Table 1
Phase III Clinical Efficacy in First-Line Treatment

	Combined Results		Paclitaxel subgroup		AC sul
	HERCEPTIN + All Chemotherapy	All Chemotherapy	HERCEPTIN + Paclitaxel	Paclitaxel	HERCEPTIN + AC[a]
	(n = 235)	(n = 234)	(n = 92)	(n = 96)	(n = 143)
Primary Endpoint					
Time to Progression[b,c]					
Median (months)	7.2	4.5	6.7	2.5	7.6
95% confidence interval	6.9, 8.2	4.3, 4.9	5.2, 9.9	2.0, 4.3	7.2, 9.1
p-value (log rank)	<0.0001		<0.0001		0.0
Secondary Endpoints					
Overall Response Rate[b]					
Rate (percent)	45	29	38	15	50
95% confidence interval	39, 51	23, 35	28, 48	8, 22	42, 58
p-value (c2-test)	<0.001		<0.001		0.
Duration of Response[b,c]					
Median (months)	8.3	5.8	8.3	4.3	8.4
25%, 75% quantile	5.5, 14.8	3.9, 8.5	5.1, 11.0	3.7, 7.4	5.8, 14.8
Survival Time[c]					
Median Survival (months)	25.1	20.3	22.1	18.4	26.8
95% confidence interval	22.2, 29.5	16.8, 24.2	16.9, 28.6	12.7, 24.4	23.3, 32.9
p-value (log rank)	0.0461		0.1746		0.1

[a] AC = anthracycline (doxorubicin or epirubicin) and cyclophosphamide.
[b] Assessed by an independent Response Evaluation Committee.
[c] Kaplan-Meier Estimate

HERCEPTIN was studied as a single agent in a multicenter, open-label, single-arm clinical trial in patients with HE overexpressing metastatic breast cancer who had relapsed following one or two prior chemotherapy regimens for disease. Of 222 patients enrolled, 66% had received prior adjuvant chemotherapy, 68% had received two prior ch regimens for metastatic disease, and 25% had received prior myeloablative treatment with hematopoietic rescue. treated with a loading dose of 4 mg/kg IV followed by weekly doses of HERCEPTIN at 2 mg/kg IV. The ORR (corr + partial response), as determined by an independent Response Evaluation Committee, was 14%, with a 2% com rate and a 12% partial response rate. Complete responses were observed only in patients with disease limited to nodes. The degree of HER2 overexpression was a predictor of treatment effect. (See CLINICAL STUDIES: *HER2 overexpression.*)

HER2 protein overexpression
Relationship to Response: In the clinical studies described, patient eligibility was determined by testing tumor spe overexpression of HER2 protein. Specimens were tested with a research-use-only immunohistochemical assay (r the Clinical Trial Assay, CTA) and scored as 0, 1+, 2+, or 3+ with 3+ indicating the strongest positivity. Only patier positive tumors were eligible (about 33% of those screened).

Data from both efficacy trials suggest that the beneficial treatment effects were largely limited to patients with the l HER2 protein overexpression (3+). (See Table 2.)

Table 2
Treatment Effect versus Level of HER2 Expression

	Single-Arm Trial	Treatment Subgroups in Randomized Trial		
	HERCEPTIN	HERCEPTIN + Paclitaxel	Paclitaxel	HERCEPTIN + AC
Overall Response Rate				
2+ overexpression	4% (2/50)	21% (5/24)	16% (3/19)	40% (14/35)

3+ overexpression	17% (29/172)	44% (30/68)	14% (11/77)	53% (57/108)
Median time to progression (months)(95% CI)				
2+ overexpression	N/A[a]	4.4 (2.2, 6.6)	3.2 (2.0, 5.6)	7.8 (6.4, 10.1)
3+ overexpression	N/A[a]	7.1 (6.2, 12.0)	2.2 (1.8, 4.3)	7.3 (7.1, 9.2)
Median Survival Time (months) (95% CI)				
2+ overexpression	N/A[a]	16.8 (11.8, 25.1)	19.8 (8.1, 28.5)	21.4 (15.0, 25.5)
3+ overexpression	N/A[a]	24.8 (18.6, 35.7)	17.9 (11.2, 23.8)	30.8 (25.8, 38.1)

[a] N/A = Not Assessed

Immunohistochemical Detection: In clinical trials, the Clinical Trial Assay (CTA) was used for immunohistochemica HER2 protein overexpression. The DAKO HercepTest™, another immunohistochemical test for HER2 protein ove has not been directly studied for its ability to predict HERCEPTIN treatment effect, but has been compared to the 500 breast cancer histology specimens obtained from the National Cancer Institute Cooperative Breast Cancer Ti Based upon these results and an expected incidence of 33% of 2+ or 3+ HER2 overexpression in tumors from wo metastatic breast cancer, one can estimate the correlation of the HercepTest™ results with CTA results. Of specir (strongly positive) on the HercepTest™, 94% would be expected to test at least 2+ on the CTA (i.e., meeting the s criterion) including 82% which would be expected to test 3+ on the CTA (i.e., the reading most associated with clir specimens testing 2+ (weakly positive) on the HercepTest™, only 34% would be expected to test at least 2+ on th including 14% which would be expected to test 3+ on the CTA.

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INDICATIONS AND USAGE
HERCEPTIN as a single agent is indicated for the treatment of patients with metastatic breast cancer whose tumc the HER2 protein and who have received one or more chemotherapy regimens for their metastatic disease. HERC combination with paclitaxel is indicated for treatment of patients with metastatic breast cancer whose tumors overe HER2 protein and who have not received chemotherapy for their metastatic disease. HERCEPTIN should only be patients whose tumors have HER2 protein overexpression. (See CLINICAL STUDIES: *HER2 protein overexpress* information regarding HER2 protein testing and the relationship between the degree of overexpression and the tre

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CONTRAINDICATIONS
None known.

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WARNINGS
Cardiotoxicity
Signs and symptoms of cardiac dysfunction, such as dyspnea, increased cough, paroxysmal nocturnal dyspnea, p edema, S3 gallop, or reduced ejection fraction, have been observed in patients treated with HERCEPTIN. Conges failure associated with HERCEPTIN therapy may be severe and has been associated with disabling cardiac failure mural thrombosis leading to stroke. The clinical status of patients in the trials who developed congestive heart failu classified for severity using the New York Heart Association classification system (I-IV, where IV is the most sever cardiac failure). (See Table 3.)

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Table 3
Incidence and Severity of Cardiac Dysfunction

	HERCEPTIN[a] alone	HERCEPTIN + Paclitaxel[b]	Paclitaxel[b]	HERCEPTIN + Anthracycline + cyclophosphamide[b]	Anthr cycloph
	n = 213	n = 91	n = 95	n = 143	n
Any Cardiac Dysfunction	7%	11%	1%	28%	
Class III-IV	5%	4%	1%	19%	

[a] Open-label, single-agent Phase II study (94% received prior anthracyclines).
[b] Randomized Phase III study comparing chemotherapy plus HERCEPTIN to chemotherapy alone, where chemot

anthracycline/cyclophosphamide or paclitaxel.

Candidates for treatment with HERCEPTIN should undergo thorough baseline cardiac assessment including histo exam and one or more of the following: EKG, echocardiogram, and MUGA scan. There are no data regarding the appropriate method of evaluation for the identification of patients at risk for developing cardiotoxicity. Monitoring m all patients who will develop cardiac dysfunction.

Extreme caution should be exercised in treating patients with pre-existing cardiac dysfunction.

Patients receiving HERCEPTIN should undergo frequent monitoring for deteriorating cardiac function.

The probability of cardiac dysfunction was highest in patients who received HERCEPTIN concurrently with anthra data suggest that advanced age may increase the probability of cardiac dysfunction.

Pre-existing cardiac disease or prior cardiotoxic therapy (e.g., anthracycline or radiation therapy to the chest) may ability to tolerate HERCEPTIN therapy; however, the data are not adequate to evaluate the correlation between H induced cardiotoxicity and these factors.

Discontinuation of HERCEPTIN therapy should be strongly considered in patients who develop clinically significar heart failure. In the clinical trials, most patients with cardiac dysfunction responded to appropriate medical therapy discontinuation of HERCEPTIN. The safety of continuation or resumption of HERCEPTIN in patients who have pr experienced cardiac toxicity has not been studied. There are insufficient data regarding discontinuation of HERCE patients with asymptomatic decreases in ejection fraction; such patients should be closely monitored for evidence deterioration.

Hypersensitivity Reactions Including Anaphylaxis

Severe hypersensitivity reactions have been infrequently reported in patients treated with HERCEPTIN. Signs and include anaphylaxis, urticaria, bronchospasm, angioedema, and/or hypotension. In some cases, the reactions hav The onset of symptoms generally occurred during an infusion, but there have also been reports of symptom onset completion of an infusion. Reactions were most commonly reported in association with the initial infusion.

HERCEPTIN infusion should be interrupted in all patients with severe hypersensitivity reactions. In the event of a reaction, appropriate medical therapy should be administered, which may include epinephrine, corticosteroids, dip bronchodilators, and oxygen. Patients should be evaluated and carefully monitored until complete resolution of sig symptoms.

There are no data regarding the most appropriate method of identification of patients who may safely be retreated HERCEPTIN after experiencing a severe hypersensitivity reaction. HERCEPTIN has been readministered to some fully recovered from a previous severe reaction. Prior to readministration of HERCEPTIN, the majority of these pa prophylactically treated with pre-medications including antihistamines and/or corticosteroids. While some of these tolerated retreatment, others had severe reactions again despite the use of prophylactic pre-medications.

Infusion Reactions

In the postmarketing setting, rare occurrences of severe infusion reactions leading to a fatal outcome have been a the use of HERCEPTIN.

In clinical trials, infusion reactions consisted of a symptom complex characterized by fever and chills, and on occa nausea, vomiting, pain (in some cases at tumor sites), headache, dizziness, dyspnea, hypotension, rash, and asth reactions were usually mild to moderate in severity. (See ADVERSE REACTIONS.) However, in postmarketing re severe adverse reactions to HERCEPTIN infusion were observed and included bronchospasm, hypoxia, and seve These severe reactions were usually associated with the initial infusion of HERCEPTIN and generally occurred du immediately following the infusion. However, the onset and clinical course were variable. For some patients, symp progressively worsened and led to further pulmonary complications. (See PULMONARY EVENTS section of WAR other patients with acute onset of signs and symptoms, initial improvement was followed by clinical deterioration. I infusion events with rapid clinical deterioration have also been reported. Rarely, severe infusion reactions culmina within hours or up to one week following an infusion.

Some severe reactions have been treated successfully with interruption of the HERCEPTIN infusion and supporti including oxygen, intravenous fluids, beta-agonists, and corticosteroids.

There are no data regarding the most appropriate method of identification of patients who may safely be retreated HERCEPTIN after experiencing a severe infusion reaction. HERCEPTIN has been readministered to some patien recovered from the previous severe reaction. Prior to readministration of HERCEPTIN, the majority of these patier prophylactically treated with pre-medications including antihistamines and/or corticosteroids. While some of these tolerated retreatment, others had severe reactions again despite the use of prophylactic pre-medications.

Pulmonary Events

Severe pulmonary events leading to death have been reported rarely with the use of HERCEPTIN in the postmark Signs, symptoms and clinical findings include dyspnea, pulmonary infiltrates, pleural effusions, non-cardiogenic pu edema, pulmonary insufficiency and hypoxia, and acute respiratory distress syndrome. These events may or may sequelae of infusion reactions. (See INFUSION REACTIONS section of WARNINGS.) Patients with symptomatic disease or with extensive tumor involvement of the lungs, resulting in dyspnea at rest, may be at greater risk of se

Other severe events reported rarely in the postmarketing setting include pneumonitis and pulmonary fibrosis.

PRECAUTIONS
General: HERCEPTIN therapy should be used with caution in patients with known hypersensitivity to Trastuzuma Hamster Ovary cell proteins, or any component of this product.

Patients with Cardiac Ventricular Dysfunction

Extreme caution should be exercised in treating patients with pre-existing cardiac dysfunction. (See WARNINGS.)

Patients with Pulmonary Disorders

Patients with either symptomatic intrinsic pulmonary disease (e.g., asthma, COPD) or patients with extensive tum of the lungs (e.g., lymphangitic spread of tumor, pleural effusions, parenchymal masses), resulting in dyspnea at r increased risk for severe pulmonary adverse events. (See WARNINGS.)

Drug Interactions: There have been no formal drug interaction studies performed with HERCEPTIN in humans. A of paclitaxel in combination with HERCEPTIN resulted in a two-fold decrease in HERCEPTIN clearance in a non-l study and in a 1.5-fold increase in HERCEPTIN serum levels in clinical studies. (See PHARMACOKINETICS.)

Benzyl Alcohol: For patients with a known hypersensitivity to benzyl alcohol (the preservative in Bacteriostatic W Injection) reconstitute HERCEPTIN with Sterile Water for Injection (SWFI), USP. DISCARD THE SWFI-RECONS HERCEPTIN VIAL FOLLOWING A SINGLE USE.

Immunogenicity: Of 903 patients who have been evaluated, human anti-human antibody (HAHA) to Trastuzuma in one patient, who had no allergic manifestations.

Carcinogenesis, Mutagenesis, Impairment of Fertility:
Carcinogenesis: HERCEPTIN has not been tested for its carcinogenic potential.

Mutagenesis: No evidence of mutagenic activity was observed in Ames tests using six different test strains of ba without metabolic activation, at concentrations of up to 5000 μg/mL Trastuzumab. Human peripheral blood lymph *in vitro* at concentrations of up to 5000 μg/plate Trastuzumab, with and without metabolic activation, revealed no e mutagenic potential. In an *in vivo* mutagenic assay (the micronucleus assay), no evidence of chromosomal damag bone marrow cells was observed following bolus intravenous doses of up to 118 mg/kg Trastuzumab.

Impairment of Fertility: A fertility study has been conducted in female cynomolgus monkeys at doses up to 25 tir human maintenance dose of 2 mg/kg HERCEPTIN and has revealed no evidence of impaired fertility.

Pregnancy Category B: Reproduction studies have been conducted in cynomolgus monkeys at doses up to 25 ti human maintenance dose of 2 mg/kg HERCEPTIN and have revealed no evidence of impaired fertility or harm to However, HER2 protein expression is high in many embryonic tissues including cardiac and neural tissues; in mut lacking HER2, embryos died in early gestation.[10] Placental transfer of HERCEPTIN during the early (Days 20-50 and late (Days 120-150 of gestation) fetal development period was observed in monkeys. There are, however, no well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of hum this drug should be used during pregnancy only if clearly needed.

Nursing Mothers: A study conducted in lactating cynomolgus monkeys at doses 25 times the weekly human mai of 2 mg/kg HERCEPTIN demonstrated that Trastuzumab is secreted in the milk. The presence of Trastuzumab in infant monkeys was not associated with any adverse effects on their growth or development from birth to 3 month not known whether HERCEPTIN is excreted in human milk. Because human IgG is excreted in human milk, and tl absorption and harm to the infant is unknown, women should be advised to discontinue nursing during HERCEPT for 6 months after the last dose of HERCEPTIN.

Pediatric Use: The safety and effectiveness of HERCEPTIN in pediatric patients have not been established.

Geriatric Use: HERCEPTIN has been administered to 133 patients who were 65 years of age or over. The risk of dysfunction may be increased in geriatric patients. The reported clinical experience is not adequate to determine v patients respond differently from younger patients.

ADVERSE REACTIONS
In clinical studies, a total of 958 patients have received HERCEPTIN alone or in combination with chemotherapy. are based on the experience with the recommended dosing regimen for HERCEPTIN in the randomized controlle 234 patients who received HERCEPTIN in combination with chemotherapy and four open-label studies of HERCE single agent in 352 patients at doses of 10-500 mg administered weekly.

Cardiac Failure/Dysfunction: For a description of cardiac toxicities, see WARNINGS.

Anemia and Leukopenia: An increased incidence of anemia and leukopenia was observed in the treatment grou HERCEPTIN and chemotherapy, especially in the HERCEPTIN and AC subgroup, compared with the treatment g chemotherapy alone. The majority of these cytopenic events were mild or moderate in intensity, reversible, and nc discontinuation of therapy with HERCEPTIN.

Hematologic toxicity is infrequent following the administration of HERCEPTIN as a single agent, with an incidence

toxicities for WBC, platelets, hemoglobin all <1%. No Grade IV toxicities were observed.

Diarrhea: Of patients treated with HERCEPTIN as a single agent, 25% experienced diarrhea. An increased incide diarrhea, primarily mild to moderate in severity, was observed in patients receiving HERCEPTIN in combination w chemotherapy.

Infection: An increased incidence of infections, primarily mild upper respiratory infections of minor clinical signific infections, was observed in patients receiving HERCEPTIN in combination with chemotherapy.

Infusion Reactions: During the first infusion with HERCEPTIN, a symptom complex most commonly consisting o fever was observed in about 40% of patients in clinical trials. The symptoms were usually mild to moderate in sev treated with acetaminophen, diphenhydramine, and meperidine (with or without reduction in the rate of HERCEPT HERCEPTIN discontinuation was infrequent. Other signs and/or symptoms may include nausea, vomiting, pain (ir tumor sites), rigors, headache, dizziness, dyspnea, hypotension, rash and asthenia. The symptoms occurred infre subsequent HERCEPTIN infusions. (See WARNINGS for information on more severe reactions reported in the po setting.)

Additional adverse reactions have been identified during postmarketing use of HERCEPTIN. Because these react reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequenc causal relationship to HERCEPTIN exposure. Decisions to include these reactions in labeling are typically based of the following factors: (1) seriousness of the reaction, (2) frequency of reporting, or (3) strength of causal connec HERCEPTIN.

Pulmonary Events
In the postmarketing setting, severe hypersensitivity reactions (including anaphylaxis), infusion reactions, and pul events have been reported. These events include anaphylaxis, angioedema, bronchospasm, hypotension, hypoxi pulmonary infiltrates, pleural effusions, non-cardiogenic pulmonary edema and acute respiratory distress syndrom detailed description, see WARNINGS.

Other adverse event(s) reported in the postmarketing setting: glomerulopathy

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Table 4
Adverse Events Occurring in ≥ 5% of Patients or at Increased Incidence in the HERCEPTIN Arm of the Rando
(Percent of Patients)

	Single Agent n = 352	HERCEPTIN + Paclitaxel n = 91	Paclitaxel Alone n = 95	HERCEPTIN * AC n = 143	AC A n =
Body as a Whole					
Pain	47	61	62	57	4
Asthenia	42	62	57	54	5
Fever	36	49	23	56	3
Chills	32	41	4	35	1
Headache	26	36	28	44	3
Abdominal pain	22	34	22	23	1
Back pain	22	34	30	27	1
Infection	20	47	27	47	3
Flu syndrome	10	12	5	12	6
Accidental injury	6	13	3	9	4
Allergic reaction	3	8	2	4	2
Cardiovascular					
Tachycardia	5	12	4	10	5
Congestive heart failure	7	11	1	28	7
Digestive					
Nausea	33	51	9	76	7
Diarrhea	25	45	29	45	2
Vomiting	23	37	28	53	4
Nausea and vomiting	8	14	11	18	9
Anorexia	14	24	16	31	2

Heme & Lymphatic					
Anemia	4	14	9	36	2
Leukopenia	3	24	17	52	3
Metabolic					
Peripheral edema	10	22	20	20	1
Edema	8	10	8	11	5
Musculoskeletal					
Bone pain	7	24	18	7	7
Arthralgia	6	37	21	8	9
Nervous					
Insomnia	14	25	13	29	1
Dizziness	13	22	24	24	1
Paresthesia	9	48	39	17	1
Depression	6	12	13	20	1
Peripheral neuritis	2	23	16	2	2
Neuropathy	1	13	5	4	4
Respiratory					
Cough increased	26	41	22	43	2
Dyspnea	22	27	26	42	2
Rhinitis	14	22	5	22	1
Pharyngitis	12	22	14	30	1
Sinusitis	9	21	7	13	6
Skin					
Rash	18	38	18	27	1
Herpes simplex	2	12	3	7	9
Acne	2	11	3	3	<
Urogenital					
Urinary tract infection	5	18	14	13	7

Other serious adverse events
The following other serious adverse events occurred in at least one of the 958 patients treated with HERCEPTIN i studies:

Body as a Whole: cellulitis, anaphylactoid reaction, ascites, hydrocephalus, radiation injury, deafness, amblyopia

Cardiovascular: vascular thrombosis, pericardial effusion, heart arrest, hypotension, syncope, hemorrhage, shock

Digestive: hepatic failure, gastroenteritis, hematemesis, ileus, intestinal obstruction, colitis, esophageal ulcer, ston pancreatitis, hepatitis

Endocrine: hypothyroidism

Hematological: pancytopenia, acute leukemia, coagulation disorder, lymphangitis

Metabolic: hypercalcemia, hypomagnesemia, hyponatremia, hypoglycemia, growth retardation, weight loss

Musculoskeletal: pathological fractures, bone necrosis, myopathy

Nervous: convulsion, ataxia, confusion, manic reaction

Respiratory: apnea, pneumothorax, asthma, hypoxia, laryngitis

Skin: herpes zoster, skin ulceration

Urogenital: hydronephrosis, kidney failure, cervical cancer, hematuria, hemorrhagic cystitis, pyelonephritis

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OVERDOSAGE
There is no experience with overdosage in human clinical trials. Single doses higher than 500 mg have not been t

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DOSAGE AND ADMINISTRATION
Usual Dose
The recommended initial loading dose is 4 mg/kg Trastuzumab administered as a 90-minute infusion. The recomr maintenance dose is 2 mg/kg Trastuzumab and can be administered as a 30-minute infusion if the initial loading c tolerated. HERCEPTIN may be administered in an outpatient setting. HERCEPTIN is to be diluted in saline for IV i **NOT ADMINISTER AS AN IV PUSH OR BOLUS**. (See ADMINISTRATION.)

Preparation for Administration
The diluent provided has been formulated to maintain the stability and sterility of HERCEPTIN for up to 28 days. C have not been shown to contain effective preservatives for HERCEPTIN. Each vial of HERCEPTIN should be rec **ONLY 20 mL of BWFI, USP, 1.1% benzyl alcohol preserved, as supplied**, to yield a multi-dose solution contair Trastuzumab. Use of all 30 mL of diluent results in a lower-than-intended dose of HERCEPTIN. THE REMAINDEI (approximately 10 mL) OF THE DILUENT SHOULD BE DISCARDED. Immediately upon reconstitution with BWFI HERCEPTIN must be labeled in the area marked "Do not use after:" with the future date that is 28 days from the c reconstitution.

If the patient has known hypersensitivity to benzyl alcohol, HERCEPTIN must be reconstituted with Sterile Water f (See PRECAUTIONS.) HERCEPTIN WHICH HAS BEEN RECONSTITUTED WITH SWFI MUST BE USED IMME ANY UNUSED PORTION DISCARDED. USE OF OTHER RECONSTITUTION DILUENTS SHOULD BE AVOIDE

Shaking the reconstituted HERCEPTIN or causing excessive foaming during the addition of diluent may result in p dissolution and the amount of HERCEPTIN that can be withdrawn from the vial.

Use appropriate aseptic technique when performing the following reconstitution steps:

- Using a sterile syringe, slowly inject **20 mL** of the diluent into the vial containing the lyophilized cake of The stream of diluent should be directed into the lyophilized cake.
- Swirl the vial gently to aid reconstitution. Trastuzumab may be sensitive to shear-induced stress, e.g., a expulsion from a syringe. **DO NOT SHAKE**.
- Slight foaming of the product upon reconstitution is not unusual. Allow the vial to stand undisturbed for a minutes. The solution should be essentially free of visible particulates, clear to slightly opalescent and c yellow.

Determine the number of mg of Trastuzumab needed, based on a loading dose of 4 mg Trastuzumab/kg body wei maintenance dose of 2 mg Trastuzumab/kg body weight. Calculate the volume of 21 mg/mL Trastuzumab solutior this amount from the vial and add it to an infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, USP **(5%) SOLUTION SHOULD NOT BE USED**. Gently invert the bag to mix the solution. The reconstituted preparatic colorless to pale yellow transparent solution. Parenteral drug products should be inspected visually for particulate discoloration prior to administration.

No incompatibilities between HERCEPTIN and polyvinylchloride or polyethylene bags have been observed.

Administration
Treatment may be administered in an outpatient setting by administration of a 4 mg/kg Trastuzumab loading dose (IV) infusion over 90 minutes. **DO NOT ADMINISTER AS AN IV PUSH OR BOLUS**. Patients should be observed chills or other infusion-associated symptoms. (See ADVERSE REACTIONS.) If prior infusions are well tolerated, s weekly doses of 2 mg/kg Trastuzumab may be administered over 30 minutes.

HERCEPTIN should not be mixed or diluted with other drugs. HERCEPTIN infusions should not be admini mixed with Dextrose solutions.

Stability and Storage
Vials of HERCEPTIN are stable at 2-8°C (36-46°F) prior to reconstitution. Do not use beyond the expiration date s vial. A vial of HERCEPTIN reconstituted with BWFI, as supplied, is stable for 28 days after reconstitution when stc

at 2-8°C (36-46°F), and the solution is preserved for multiple use. Discard any remaining multi-dose reconstituted 28 days. If unpreserved SWFI (not supplied) is used, the reconstituted HERCEPTIN solution should be used imm unused portion must be discarded. DO NOT FREEZE HERCEPTIN THAT HAS BEEN RECONSTITUTED.

The solution of HERCEPTIN for infusion diluted in polyvinylchloride or polyethylene bags containing 0.9% Sodium Injection, USP, may be stored at 2-8°C (36-46°F) for up to 24 hours prior to use. Diluted HERCEPTIN has been sl stable for up to 24 hours at room temperature (2-25°C). However, since diluted HERCEPTIN contains no effective the reconstituted and diluted solution should be stored refrigerated (2-8°C).

HOW SUPPLIED

HERCEPTIN is supplied as a lyophilized, sterile powder nominally containing 440 mg Trastuzumab per vial under

Each carton contains one vial of 440 mg HERCEPTIN® (Trastuzumab) and one 30 mL vial of Bacteriostatic Wate USP, 1.1% benzyl alcohol. NDC 50242-134-60.

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4817403
Revised December 2001